

Title: Unraveling the Biological Basis for Domain-Specific Cognitive Decline: A Commentary on "Neural Basis of Cognitive Assessment in Alzheimer's Disease, Amnestic Mild Cognitive Impairment, and Subjective Memory Complaints"

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Nearly all diagnoses of dementia or cognitive impairment, regardless of underlying pathology, depend on neuropsychological evaluation. Targeted tests, evaluating memory, executive function, attention, language, and visuospatial processing, among other domains, are commonly used to better understand the cognitive changes in older adults presenting with cognitive decline. The cognitive domain-specific pattern of deficits in any dementia evaluation can give important information about the disease and inform the diagnostic process and suggest underlying pathology. Thus, a better understanding of these tests and the underlying brain networks and regions that are essential for successful execution of these tests could help to inform clinicians about the potential anatomical patterns of degeneration that a patient may be experiencing.

In Matias-Guiu et al., the associative brain changes of a wide variety of cognitive tests, representing a comprehensive test battery across cognitive domains, is explored. They correctly point out that despite the fact that many cognitive tests are considered to test exclusively a single cognitive domain (i.e., memory, executive function, etc.), many tests tap into multiple cognitive brain networks. Thus, using a cohort spanning the continuum between healthy aging, mild cognitive impairment (MCI), and mild Alzheimer's disease (AD) dementia, Matias-Guiu et al. evaluated test-specific patterns of association with glucose metabolism measured using [ $^{18}\text{F}$ ]fluorodeoxyglucose (FDG) positron emission tomography (PET). The goal was to determine the distributed networks of neuronal activity that are linked to changes in cognition.

The findings in Matias-Guiu et al. support previous findings from functional MRI and PET studies suggesting broad but domain-specific patterns of activity during cognitive tasks. In Matias-Guiu et al., decline in the Boston Naming Test (BNT), a measure of confrontational word retrieval, was associated with lower glucose metabolism in bilateral but left dominant regions of the lateral temporal and inferior frontal lobes. Previous studies have implicated many of these regions in semantic fluency and language, including the dorsal and ventral language networks [1, 2].

Episodic memory was tested in Matias-Guiu et al. using the Free and Cued Selective Reminding Test (FCSRT). Impairment in the FCSRT was associated with reduced glucose metabolism in the medial temporal lobe, including the parahippocampal gyrus, posterior cingulate, precuneus, and middle temporal gyrus. The medial temporal lobe and the posterior cingulate/precuneus have been implicated in a number of fMRI studies of episodic memory, with altered activation in these regions reported in both prodromal and clinical AD [3-5].

Visuospatial function and executive function were tested using the Rey-Osterrieth Complex Figure copying task, Trail Making Part A and B, and the Tower of London test. Visuospatial function was also tested using the Visual Object and Space Perception (VOSP) Battery. Finally, visual scanning and attention were assessed using the Symbol Digit Modalities Test. Decreased performance on each of these tests was independently associated with widespread areas of glucose hypometabolism in Matias-Guiu et al.

Specifically, in Matias-Guiu et al., the Rey-Osterrieth Complex Figure copying task was associated with primarily bilateral parietal, temporal, and occipital regions, with greater association in the right than left hemisphere. The findings support the role of the parietal and occipital lobes in visuospatial perception and processing, as has been previously noted with other visuospatial tests [6]. The right vs. left asymmetry is notable, as the right hemisphere has been linked with spatial relations, which are likely an important part of successful completion of

this task [7-9]. Thus, the findings from Matias-Guiu et al. support the role of the visuospatial neural processing network of regions (parietal, temporal, occipital) in successful performance on the Rey-Osterrieth Complex Figure task.

The Trail Making Test Parts A and B were associated with glucose metabolism in widespread regions of the cortex, primarily in posterior regions in Matias-Guiu et al. The identified regions included the middle temporal gyrus and fusiform, which were previously implicated as involved in the Trail Making Test in an fMRI study of a similar test [10], among other temporal, parietal, and occipital regions. Some hemispheric differences were again observed, with the right hemisphere showing a more extensive association, likely due to the visuospatial processing component of the test. The Tower of London also showed association in the posterior cortical regions, including the parietal, occipital, and posterior temporal regions in Matias-Guiu et al. These findings show overlap with an fMRI study of the Tower of London task, specifically in the parietal and frontal cortices [11]. However, both the Trail Making Test and Tower of London were associated with more regions in Matias-Guiu et al. than previously implicated in fMRI studies. This finding may suggest that some of the observed associations are disease-specific (i.e., due to AD) and not necessarily specific to the task. In fact, most of the cognitive task associations implicated the lateral parietal lobe as an area of interest. However, AD and MCI patients have been shown to have glucose hypometabolism in these regions relative to cognitively normal older adults, suggesting these associations might be partially due to disease effects rather than cognitive task specific effects [12, 13].

Visuospatial function on the VOSP and visual scanning and attention on the Symbol Digit Modalities Test was associated with glucose metabolism in many of the same temporal, parietal, and occipital regions seen in the Rey-Osterrieth Complex Figure task, Trail Making Test, and Tower of London in Matias-Guiu et al. For the most part the various sub-tests within the VOSP were associated with overlapping posterior cortical regions. Again, the parietal and occipital associations of these two tests support the visuospatial processing aspects of the tasks [14, 15].

In sum, the findings in Matias-Guiu et al. provide important information about the biological underpinnings of domain-specific cognitive impairment in normal aging and in MCI and AD patients. Many previous studies have evaluated one or two cognitive domain associations with glucose metabolism or using fMRI, but few have looked across the cognitive domains tested in Matias-Guiu et al. in the same cohort of patients. The distributed nature of many of the associations further supports the idea that many cognitive tests used clinically involve multiple cognitive systems representing a widespread anatomic territory. These findings help to inform clinicians and neuropsychologists about the nature and interpretation of results from these tests and support the importance of understanding the biological and anatomical basis for deficits.

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